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MEDICINE

October 23, 1997

Larry G. Hart, M.D.
111 Alexander Drive
Building 101
Research Triangle Park, NC 27709

Dear Dr. Hart,

It is my understanding the National Toxicology Program Board of Scientific Counselors will be holding a public meeting on October 30 and 31 to discuss the possible listing of tamoxifen for the 9th *Report on Carcinogens*. The *Federal Register* announcement (October 2, 1997, volume 62, number 191) encourages submission of information on studies of human exposure to tamoxifen. As I have just recently completed a study of the effects of tamoxifen therapy for breast cancer on the subsequent risk of endometrial cancer that is, I believe, relevant to your deliberations, I am submitting this letter in lieu of an oral presentation.

As is apparent from my letterhead, I am a professor of preventive medicine at the University of Southern California and the scientific director of the population-based cancer registry for Los Angeles County, which is one of the Surveillance, Epidemiology and End Results (SEER) registries funded by the National Cancer Institute (NCI). I am trained as a biostatistician, but have spent much of my career studying the etiology of breast and other cancers. I have also conducted several studies of the cancer treatment induced risk of subsequent primary cancers.

The basis for the consideration of tamoxifen as a human carcinogen has been epidemiologic studies in which the endometrial cancer risk of breast cancer patients treated with tamoxifen has been compared to that of breast cancer patients who were not treated with tamoxifen. One of the more recently published studies that is often cited as definitive, utilized information on breast cancer treatment collected by the SEER registries (Curtis et al, 1996). SEER data on first course of treatment are known to be incomplete. In this study, the designation that a woman received tamoxifen therapy is based on cancer registry reporting that the woman's first course of treatment included treatment with a hormonal preparation. It did not differentiate between hormonal treatments. By virtue of the available information, it ignored treatment that was not considered as the "first course of treatment." No direct evidence was obtained in this study to verify that "exposed" women received tamoxifen therapy and that "unexposed" did not. This study provided no data on dose or duration of exposure.

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Studies designed to look more carefully at this issue have been the case-control studies nested within cancer registration systems, where information was sought as to whether cases (breast cancer patients later diagnosed with endometrial cancer) and controls (breast cancer patients with an intact uterus and no subsequent cancer diagnosis) had received tamoxifen therapy. The most definitive of these (van Leeuwen et al, 1994) showed an increase in endometrial cancer risk with increasing duration of tamoxifen therapy; however, because of small numbers of exposed study subjects, the results were of borderline statistical significance.

Clinical trials have provided some additional evidence of a tamoxifen effect, but in evaluating results from these, one must consider that they were not designed to assess this association; as concerns have grown since the mid to late 1980s with regard to the possible effects of tamoxifen on the endometrium, women receiving tamoxifen on these trials may have been subjected to more intense screening than women receiving other treatments. Since these trials tend to be community-based (e.g., the NSABP B-14 trial), it is difficult to guard against the potential effects on results of such an "unmasking bias."

Most importantly, however, none of the published studies of the effects of tamoxifen therapy on subsequent endometrial cancer risk has adequately addressed the joint or modifying effects of other accepted endometrial cancer risk factors (prior use of estrogen replacement therapy and oral contraceptives, and obesity). The NCI-funded study that we have recently completed was specifically designed to take these factors into account. As our results are not yet submitted for publication, I will briefly describe the design and results.

The study utilizes a design similar to that of van Leeuwen and colleagues (1994). We conducted a case-control study within 4 SEER registries (Los Angeles - 228 cases/486 controls; Iowa - 50 cases/95 controls; Seattle - 34 cases/62 controls; and Atlanta 14 cases/28 controls) identifying case and control patients diagnosed with breast cancer between 1978 and 1992. Case patients were women diagnosed with endometrial cancer at least six months after their diagnosis of invasive breast cancer which was their first primary cancer diagnosis. Control patients were carefully matched to cases on year of breast cancer diagnosis, year of birth, race (White, Black, Asian), residence in the registry region and breast cancer summary stage (local, regional or metastatic disease). Control patients were required to have survived to the date of the matched case patient's endometrial cancer diagnosis. Control patients must have had an intact uterus when the case patient was diagnosed with endometrial cancer. Both case and control patients must have lived in the registry region during the "at risk" interval and had no cancer diagnoses other than possibly a second primary breast cancer. Patients (and in some instances, next of kin) were interviewed to obtain information on some possible risk factors and to create a roster of physicians seen for breast cancer treatment as well as other physicians seen during adulthood (internists, gynecologists, family practitioners as well as some other specialists). Hospital and physician medical records were abstracted for information on tamoxifen and other breast cancer therapy, and the use of hormonal preparations (oral contraceptives, estrogens and progestins). Body weight was obtained from the hospital medical record at the time of the initial breast cancer diagnosis.

In this study, we observed the expected statistically significant duration-response relationship between prior use of estrogen replacement therapy and endometrial cancer risk. Similarly, endometrial cancer risk increased significantly with increasing body mass index. Women who had used oral contraceptives were at reduced risk.

Tamoxifen use was associated with a statistically significant increased risk of endometrial cancer among these women. Looking at the duration-response relationship for tamoxifen, our risk estimates are quite similar to those published by van Leeuwen et al (1994) (trend p=0.001). However, these effects were dramatically modified by whether or not the woman was obese and whether or not she had previously used estrogen replacement therapy. Among thin women and those who had no prior history of taking estrogen replacement therapy, the effects of tamoxifen were muted and, although risk estimates increased somewhat with increasing duration, the trend in risk was not statistically significant (p=0.29). Among women who were above the median of controls in terms of body mass index and who had taken estrogen replacement therapy, the tamoxifen-associated risk of endometrial cancer rose dramatically (trend p<0.0001). The duration effects of tamoxifen use on thin women with a history of estrogen use (trend p=0.01) and obese women with no estrogen use (trend p=0.04) were intermediate to those of the unexposed or "doubly exposed" groups. Overall, the results of our study suggest that both endogenous and exogenous estrogens substantially modify the effects of tamoxifen on endometrial cancer risk. This study also indicates the results of previous studies must be considered in light of the fact that they estimate risk across groups of women at varying levels of underlying endometrial cancer risk.

Thank you for the opportunity to comment on this issues.

Sincerely,

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Senior Associate Dean, School of Medicine